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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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07/05/2001

Yuta Nakai

US-1420

1677

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EXAMINER

MARVICH, MARIA

ART UNIT

PAPER NUMBER

1633

NOTIFICATION DATE

DELIVERY MODE

10/13/2010

ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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<p align="center">Advisory Action Before the Filing of an Appeal Brief</p>	<p>Application No. 09/897,988</p>	<p>Applicant(s) NAKAI ET AL.</p>	
	<p>Examiner MARIA B. MARVICH</p>	<p>Art Unit 1633</p>	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 13 September 2010 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
- b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
- (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
- (b) ☐ They raise the issue of new matter (see NOTE below);
- (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
- (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
- The status of the claim(s) is (or will be) as follows:
- Claim(s) allowed: _____.
- Claim(s) objected to: _____.
- Claim(s) rejected: 1,6 and 12-17.
- Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because:
See Continuation Sheet.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☒ Other: IDS filed 9/14/10. As well, the status of the claims is corrected from the 326 filed 6/11/10.

/Maria B Marvich/
Primary Examiner, Art Unit 1633

Continuation of 11. does NOT place the application in condition for allowance because: Applicants' arguments filed 9/13/10 have been considered but are not persuasive for the following reasons.

Applicants provide arguments and evidence that improved growth yield does not lead to improved production of L-amino acids. Applicants' arguments to this end are related to teachings presented as evidence.

Exhibit # 1- Eggeling et al is said to disclose that L-lysine excretion is improved by limiting growth. However, these teachings are not commensurate with the instant teachings. Specifically, Eggeling et al are directed towards methods of improving L-lysine production in *Corynebacterium glutamicum*. To this end, applicants approach, distinct from that of the instant art, is to overexpress individual biosynthetic genes and discover that *dapA* alterations affect lysine markedly. In this specific instance flux is improved concomitant with improved L-lysine production is a growth limitation.

This does not only achieve an increase in lysine yield but THIS EXAMPLE of an intracellularly introduced growth limitation is proposed as a new general MEANS OF INCREASING FLUX for industrial metabolite over-production (emphasis added).

These arguments appear directed against Kusomoto which teaches that

"in order to improve the efficiency of cell growth and amino acid production, it is important to understand the aerobic energy metabolism or, more specifically, the respiratory proton pumps in the bacterium."

"Cytochrome *bd*-type oxidase has been shown to have a lower H₂/O ratio than haem-copper oxidases (Miller and Gennis 1985; Puustinen et al. 1991). It has been reported that the H₂/e-ratio is about 1 for intact cells of *C. glutamicum* with endogenous substrate. This is lower than that expected if an *aa3*-type haem-copper oxidase is operating (Kawahara et al. 1988). Thus, it is likely that deletion of the cytochrome *bd* genes would increase the H₂/e ratio of the respiratory chain, the efficiency of energy metabolism, and consequently the growth yield of the bacterium."

Neither of these teachings of Eggeling et al nor Kujima et al are directed to generic teachings that suggest that any alteration produces growth limitation /improvement and an increase in L-lysine. Rather, each conclusion stands on its own merits. This is to say the Kujima et al teach that the specific teachings of improved energy efficiency lead to improved growth yield and improved L-amino acid production. The methods and processes and conclusions are unrelated to Eggeling et al.

Exhibit #2- Hollander et al, teaches methods of improving L-lysine wherein phosphorus and/or carbon sources are limited. Hollander et al teach that the limitation of phosphorous/ carbon is directly responsible for reduced biomass (see e.g. col 3, line). In fact, figure 1 demonstrates that as biomass increases so does the yield of L-lysine unless carbon and/or phosphorus is limited (figure 2 and 3). Therefore, neither of Eggeling et al or Hollander et al provides adequate elucidation of recombinant engineering methods related to improved energy efficiency and growth requirements. Rather, Eggeling et al alter an enzyme in the biosynthetic pathway related to L-lysine production. The effect of this mutation is to lower growth yield. One can propose a number of means by which the two phenotypes occur for example the effect of increasing one branch point, *dapA* is to lower other biosynthetic pathways such that the growth yield is the effect of the modification and is not necessarily involved in the yield.

In essence, applicants argue that art exist that teaches that the combination is unsatisfactory for the intended purpose. However, "[k]nown disadvantages in old devices which would naturally discourage search for new inventions may be taken into account in determining obviousness." *United States v. Adams*, 383 U.S. 39, 52, 148 USPQ 479, 484 (1966). (MPEP 2145, D, 3). In this case, the method of recombinant engineering of Hollander et al and Eggeling et al differ significantly from that of Kujima et al wherein ancillary effects in the growth rate would not necessarily be the same for both. In the case of Hollander et al the limitation on biomass is a consequence of limiting carbon and/or phosphorous which step is not utilized in the instant rejection. In the case, of Eggeling et al, the limits on growth are a consequence of the recombinant techniques utilized to overexpress *dapA*, which methods are not part of the instant rejection. To this end, the MPEP 2145 teaches, "In re Huang, 100 F.3d 135, 139-40, 40 USPQ2d 1685, 1689 (Fed. Cir. 1996). See also GPAC, 57 F.3d at 1580, 35 USPQ2d at 1121; In re Paulsen, 30 F.3d 1475, 1482, 31 USPQ2d 1671, 1676 (Fed. Cir. 1994) (Evidence of commercial success of articles not covered by the claims subject to the 35 U.S.C. 103 rejection was not probative of nonobviousness.). Additionally, the evidence must be reasonably commensurate in scope with the claimed invention. See, e.g., In re Kulling, 897 F.2d 1147, 1149, 14 USPQ2d 1056, 1058 (Fed. Cir. 1990); In re Grasselli, 713 F.2d 731, 743, 218 USPQ 769, 777 (Fed. Cir. 1983). In re Soni, 54 F.3d 746, 34 USPQ2d 1684 (Fed. Cir. 1995) does not change this analysis. In *Soni*, the Court declined to consider the Office's argument that the evidence of nonobviousness was not commensurate in scope with the claim because it had not been raised by the examiner (54 F.3d at 751, 34 USPQ2d at 1688)."

Rather, the instant rejection improves energy yield by recombinant methods of altering energy pathways, a technique that is unrelated to the methods of Hollander et al or Eggeling et al. In so doing, the energy yield of the cell is improved, amino acid production is improved and growth yield is improved.